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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/087,136	05/28/1998	H. ROBERT HORVITZ	01997/202002	9188

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 05/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/087,136	HORVITZ ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,4-7,10-18,25,34,36,38-40,42,44-46,48,50-52,54,56-58,60,61,63 and 64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/18/2000*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,4-7,10-18,25,34,36,38-40,42,44-46,48,50-52,54,56-58,60,61,63 and 64.

DETAILED ACTION

1. Claims 1, 10, 16, 17, 18, 25, 34, 38-40, 44, 45, 46, 50-52, 56-58 and 61 have been amended. Claims 35, 37, 41, 43, 47, 49, 53, 55, 59 and 62 have been canceled. Claims 1, 4-7, 10-18, 25, 34, 36, 38-40, 42, 44-46, 48, 50-52, 54, 56-58, 60, 61, 63 and 64 are pending and under consideration.

2. Sections of Title 35 U.S. Code, not found in this action can be found in a prior action.

3. The rejection of claims 1, 4-7, 10-18, 25, 34, 36, 38-40, 42, 44-46, 48, 50-52, 54, 56-58, 60, 61, 63 and 64 under 35 U.S.C. 101 for lacking a specific, substantial asserted utility or a well-established utility is maintained. The rejection of claims 1, 4-7, 10-18, 25, 34, 36, 38-40, 42, 44-46, 48, 50-52, 54, 56-58, 60, 61, 63 and 64 under 112, first paragraph for lacking enablement because one of skill in the art would not know how to use the products of the instant invention in a specific and substantial utility is also maintained.

The claims are drawn to nucleic acids encoding a lineage-37 polypeptide, wherein said lineage-37 polypeptide has 85% sequence identity to SEQ ID NO:1, is hydrophilic, acts non-cell autonomously, and inhibits cell proliferation.

The specification states (page 17, lines 4-7) that lin-37 is a novel synMuv gene consisting of SEQ ID NO:1 and encoding the protein of SEQ ID NO:2. The specification has disclosed the sequence of the coding regions of two existing lin-37 alleles, n758 and n2234, the first of which is a null allele and the second of which encodes a truncation mutant (page 20, lines 20-23). The specification teaches that a lin-37:GFP transgene was expressed broadly in embryos and in hypodermal cells and vulval cells through larval development consistent with a "non-autonomous" site of action (page 20, line 23 to page 21, line 3). The "non-autonomous" action of lin-37 was corroborated by Hedgcock et al (Genetics, 1995, Vol. 141, pp. 989-1006, reference of the IDS submitted December 14, 1999). The specification defines a "SynMuv" gene as encoding a polypeptide which either inhibits or enhances cell death (page 9, lines 10-12). The specification states that modulating or altering cell proliferation means that the number of cells which undergo cell division in a given population of cells is increased or decreased, or that the fate of a given cell is altered (page 10, lines 8-10). The specification states that compounds

which block the Muv phenotype of a synMuv mutant animal are potential antitumor agents and that compounds which stimulate cell division in animals with a single silent synMuv mutation are likely to be antagonists of cell proliferation and may act in a manner analogous to growth factors (page 19, lines 12-16). The specification states that "experiments which stem directly from this research include searches for mammalian homologues of the novel synMuv genes" and that such homologues "may function in activating, enhancing or otherwise intensifying the effects of tumor suppressors or oncogenes in mammals" (page 19, lines 3-6). The specification states that candidate SynMuv modulators include peptide as well as non-peptide molecules and that modulators "found to be effective at the level of SynMuv expression or activity may be confirmed as useful for [either] the inhibition of cell death". The specification states that lin-37does not have homology to known tumor suppressor genes (page 18, lines 6-8) but proposes that the SynMuv genes are involved in the negative regulation of the Ras pathway that mediates vulval induction in C elegans (page 19, lines 21-24). The specification has not identified a Ras pathway in mammals which would be orthologous to the Ras pathway of the nematode, nor does the specification teach how the commitment of cells to vulval induction in the nematode has a nexus to a biochemical signaling pathway in mammals that would be causative, rather than associative, with the cancerous phenotype in mammals. The general teachings of the art do not assist in identifying a specific Ras pathway in mammals, because specific, not general teachings are required. The art teaches the lin-37 gene by means of genetic mapping rather than as an isolated gene or protein (Ferguson et al, Genetics, 1989, Vol. 123, pp. 109-121, , reference of the IDS submitted December 14, 1999, for example, figure 1B). The art teaches that lin-37 are class B mutations, but that said class B mutants do not have a detectable phenotype, and are ascribed to silent Muv mutations (page 112, second column, lines 14-16). The art teaches that the activity of one complex of genes, or signaling pathway of genes is disrupted by class A mutation, while the activity of a second complex or pathway is disrupted by class B mutations. The art teaches that the pathways are functionally redundant and that it is necessary to have double mutants containing both class A and class B mutations in order to observe a Muv phenotype (page 118, second column, lines 2934). The art teaches that a molecular analysis of these genes and their products should help reveal why these pathways are functionally redundant and how these genes act to control vulval cell fate (page 120, first column, lines 23-26). The art provides no teachings

by which to relate to a specific Ras signaling pathway which is associated with the cancerous phenotype in mammals.

Applicant has argued that it is well known in the art that genes from C elegans have previously been used to isolate human orthologous genes. Applicant currently argues that one of the instant inventors was awarded the Nobel Prize for "confirming great benefit on mankind". the examiner would like to point out that the requirements for a Nobel Prize and a US patent are quite different. The Nobel prize being awarded for a lifetime of research and the stimulation of subsequent research by others. The requirements for satisfying 35 U.S.C. 101 are based on the instant application alone. Further, there is no nexus between the discoveries of human genes made by identifying homologs of C elegans genes and the patentable utility of the instant lin-37. Each gene is a separate product encoding proteins having separate functions. Further, the instant specification has not provided any teachings regarding how to identify an ortholog of lin-37 in a mammal: without knowing the corresponding Ras pathway in humans in which the lin-37 homolog would be a part, one of skill would not be able to identify said orthologs The instant specification does not provide a nexus between the lin-37 gene or a SynMuv gene or gene product and another C elegans gene or gene product which has in itself a specific and substantial utility. In the absence of any disclosed correlation between the claimed polynucleotide or the protein that is encoded thereby to any specific disease, or mammalian Ras pathway, any information obtained by isolating a mammalian homolog or ortholog would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." Brenner, 148 USPQ at 696.

4. In the event applicant can overcome the rejection under 101 above, the following rejections will apply:

Claims 1, 4-7, 10-15, 25, 34, 36, 38-40, 42, 44, 45, 58, 60, 61, 63 and 64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids encoding SEQ ID NO:1, and isolated cells comprising SEQ ID NO:1 does not reasonably provide enablement for nucleic acids encoding a polypeptide having at least 85% sequence identity to SEQ ID NO:1, or cells within an organism having received said lin-37 nucleic acid by

means of a gene therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

(A) As drawn to nucleic acids encoding variant lin-37 polypeptides

The instant claims are drawn to nucleic acid molecules encoding a lin-37 polypeptide, said polypeptide having 85% amino acid sequence identity to SEQ ID NO:1 wherein said polypeptide is hydrophilic, acts non-cell autonomously and inhibits cell proliferation. The specification has set forth SEQ ID NO:1 as encoded by SEQ ID NO:2. The specification has also set forth a null allele of SEQ ID NO:2 and a truncation mutant of SEQ ID NO:2, nether of which would be expected to encode a proteins which has the same function as SEQ ID NO:1 with regard to the inhibition of cell proliferation. In order to satisfy the requirements of 112, first paragraph, the specification must be enabling for how to make and how to use the broadly claimed nucleic acids. Because the instant specification has not satisfied the requirement of 35 U.S.C. 101, it has also not shown how to use said polypeptides in a specific and substantial utility. However, for the purpose of the instant rejection, that issue will be held in abeyance until such time as applicant overcomes the rejection under 101. However, the specification lacks enablement for how to make said polypeptides having the claimed characteristics. The specification states that "experiments which stem directly from this research includes searches for mammalian homologues of the novel synMuv genes". However, the isolation of a homologous genes is not commensurate with "how to make" a gene encoding a protein having at least 85% sequence identity to SEQ ID NO:1. The specification has not taught domains of SEQ ID NO:1 which are responsible for the inhibition of cell proliferation or the non-autonomous action of SEQ ID NO:1. Further, even if said domains were disclosed by the specification, the specification has not taught regions of SEQ ID NO:1 which would tolerate amino acid substitutions. It is noted that the claim reads on 85% amino acid in ditty to SEQ ID NO:1 and is not limited to conservative amino acid substitutions. The art teaches that. protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, as disclosed by Burgess et al (Journal of Cell Biology, 1990, Vol. 111, pp. 2129-2138), replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein.. As

another example, replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. (Lazar et al, 1988, Molecular and Cellular Biology Vol. 8, pp. 1247-1252). These references demonstrate that even a single amino acid substitution or what appears to be a minor chemical modification will often dramatically affect the biological activity and characteristic of a protein. Clearly, it could not be predicted that a protein variant having 85% sequence identity with SEQ ID NO:1 will function as suggested. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make/use variants of SEQ ID NO:1 which will function as SEQ ID NO:1. Given the lack of specific teachings in the specification, one of skill in the art would be subject to undue experimentation without reasonable expectation of success n order to make and use the broadly claimed nucleic acids.

(B) As drawn to cells which are not isolated cells, but part of an organism

Claims 16-18, 46, 48, 50-52, 54, 56 and 57 are drawn to cells comprising the lin-37 nucleic acids and transgenic cells comprising the lin-37 nucleic acids.

The specification teaches that the synMuv genes are useful in gene therapy to modulate cell proliferation (page 30, lines 1-4). The specification states that SynMuv mRNA may be administered to malignant cells by viral vectors, direct nucleic acid administration, lipofection, gene therapy constructs, and regulation through cognate regulatory sequences (page 30, line 5 to page 32, line 6). Thus, the instant specification contemplates the transfer of the lin-37 nucleic acid by gene therapy means into an organism. The specification is not enabling for gene therapy for the following reasons:

The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors comprising said nucleic acids. The state of the art is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242, cited in Paper No. 10) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101, cited

Paper No. 10) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

As of the priority date sought, it was well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and as of the priority date sought, highly unpredictable in view of the complexity of in vivo systems. Orkin et al state ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995, cited in Paper No. 10) that clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), thus encompassing the instant claims drawn to the administration of antigen presenting cells transfected or infected ex vivo. Orkin et al concludes that, "none of the available vector systems is entirely satisfactory, and many f the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that the level and consistency of expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a

specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

The specification does not remedy any of the deficiencies or the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues pointed out by Verma or Eck or Orkin. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the methods of claims.

5. All other rejections and objections as set forth in the previous Office action are withdrawn.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
05/16/2004

KAREN A. CANELLA, PH.D
PRIMARY EXAMINER